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Renal Replacement Therapy: Challenge on the Best Therapeutic Modality

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Introduction

Before 1970, therapeutic modalities for patients with end-stage renal disease (ESRD) were limited and a small number of patients underwent regular dialysis because few dialysis facilities were available. Patients had to be screened for the eligibility of maintenance therapy, and treatment was offered merely to patients who had renal failure as the predominant clinical feature. Kidney transplantation was in the early stages of development as a preferable therapeutic approach and most patients thought that the diagnosis of chronic renal failure corresponds to death.

Fortunately, in recent decades, the availability of care for patients with kidney failure rolled out rapidly throughout the developing countries. For example, in Iran, ESRD population consists of 32,686 patients who approximately half of them (49%) has received kidney transplant and the remainder has undergone dialysis therapy (48% hemodialysis and 3% peritoneal dialysis) [1] compared to, 91% of the incident U.S. ESRD population who were treated with hemodialysis, 7% by peritoneal dialysis and 2% by preemptive transplantation [2].

The greatest growth has occurred in the kidney transplant population, at 5–6 percent each year since 2001; in the year 2008, however, this growth slowed to 4.4 percent. The number of patients who received a kidney transplant as their first renal replacement therapy reached 2,641 in 2007 and then fell to 2,644 in the year 2008 [2]. Despite numerous medical and technical advances, patients with renal failure on dialysis often remain unwell. For most patients with renal failure, renal transplantation has the greatest potential for restoring a healthy, productive life. However, all transplant recipients have been exposed to the adverse consequences of chronic kidney disease (CKD) which can impact on the overall health of renal transplantation candidates.

Incidence and Prevalence of ESRD

The worldwide dialysis population has been reported to reach approximately 2 million subjects in the 2010 [2]. The highest prevalence rate for ESRD is found in Japan at 2045 per million and then by the United States at 1509 per million population [3,4]. These high numbers reflect the policies of these two nations to provide open access to chronic dialysis therapy and nearly universal health care for patients with ESRD. The worldwide prevalence rates of ESRD varies greatly, with less than 10 per million population reported by several countries. Currently, 52% of the global dialysis population resides in just four countries (United States, Japan, Germany and Brazil) that make up only 11% of the world population [3]. The occurrence of ESRD varies widely between different countries and also within different regions of the same country. Wide differences in access to treatment, the availability of specific modalities of therapy and methods of reimbursement between nations likely accounts for the broad ranges of reported ESRD prevalence.

It must be considered that international comparison of incidence and prevalence rates may be complicated by different definitions of ESRD and in the classification of the underlying cause of kidney failure, as well as by variability in the accuracy of the reported data. However,

within these limitations, the increase in ESRD in Europe has mirrored the U.S. experience; although absolute rates are lower. The incidence rates in Western Europe increased linearly by approximately 4.8% per year [5]. As occurred in the United States, rates increased faster in men than in women and were more marked in older age groups [6]. The annual incidence rate of ESRD in Japan increased roughly threefold between 1982 and 2001.

The unadjusted rate in Taiwan is similar to that of the United States and has continued to increase at almost double the U.S. rate over the last several years [7]. The unadjusted incidence rate in Australia and New Zealand is considerably less than the aforementioned rates [8]. Compared to the U.S. rate, lower incidence of ESRD in some countries, may be attributed to the high incidence of ESRD in blacks in the United States. It is also clear that CKD prevalence rates are substantial in countries with low income in which ESRD treatment is very limited or not available, such as Pakistan [9]. The prevalence of ESRD in the United States has grown consistently over the last several decades, as a result of both the increased incidence rate and better survival rates. Improved survival rates have contributed to the increased number of prevalent patients on dialysis. However, more recently, as seen with the incidence rate, the rate of increase has stabilized, with recent annual increases of approximately 5% per year. The annual rate of growth has slowed in the prevalent hemodialysis population, from 8.7 percent in 1997 to 3.7 percent in 2008, while the prevalent peritoneal dialysis population rose 1.3 percent in 2008, the first increase since 2003 [2].

Furthermore, even with the stabilization of the incidence rate, on the basis of the anticipated demographic changes in general population and of the sustained increase in diabetes, it is estimated that, by 2015, the incidence (95% CI) rate for ESRD will have increased to 136,166 cases per year [10]. The incidence of renal replacement therapy will vary with the prevalence of CKD in the general population, the rate of progression of CKD to ESRD, the rate of acceptance of patients onto renal replacement programs and effects of competing causes of mortality, which result in the death of patients prior to the initiation of dialysis. Furthermore, the relative impact of these different factors with regard to increasing incidence may differ substantially by race [11].

Therapeutic modalities for the ESRD are various among countries. For instance, in the United Kingdom, Australia, and Canada, home

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dialysis is used extensively, whereas this modality is uncommon in Japan [7]. Furthermore, renal transplantation varies considerably among countries. Religious believe and tent; legal constraints and cultural barriers to the acceptance of brain-death criteria or living donation are important determinants of national transplantation rates. Although viewed as negative, death is inevitable and eventually occurs for everyone. In several religions, death is believed by some to open the door to a new spiritual realm. It is for this reason that Judeo-Christian, Tibetan Book of the Dead, Buddhist and Methodist tenets, for example, permit patients to refuse therapy [12].

Demographics of ESRD population

The United States Renal Data System (USRDS) reports updated demographic information about the ESRD each year. In March 2002, 275,000 patients underwent maintenance dialysis in the United States which increased to 520,000 in the year 2010 [13]. The average age of patients on dialysis is increasing so that approximately half of them are older than 65 years. Developing countries, in particular, are generally characterized by a lower age of the general population and, in addition, the average age of a patient commencing dialysis is considerably lower there than in developed countries. Traditionally, older subjects, especially those with significant comorbidities, may not have been offered or may not have been willing to accept dialysis. More recently, whether because of better management of comorbidities, higher patient expectations, or greater availability of renal replacement therapy, this has substantially changed.

Moreover, ESRD is more common in men (53% male, 47% female) and black race. The race- and age-adjusted incidence of ESRD is higher in men than in women; a differential that has increased over time. However, whether the lower incidence of ESRD in women relative to men represents a true biologic effect of gender or is the result of underdiagnosis or undertreatment of ESRD in women requires further evaluation. Furthermore, adjusted ESRD incidence rate differs substantially by race, with African Americans having a 3.5-fold higher age- and gender-adjusted incidence rate than do whites [7].

Substantial geographical variability also exists in the ESRD incidence rate, with higher rate in urban than in rural settings. This may be due to a movement of patients on treatment from rural to urban environments or to limited access to care in rural settings, with reduced opportunities for disease recognition and management.

Diabetes mellitus and hypertension are the most common causes of ESRD (40% and 28%, respectively). Table 1 shows the underlying etiology of chronic kidney disease in the United States, Iran and Saudi Arabia [14]. It seems that CKD of unknown etiology is more frequently observed in developing countries, because of late referral of patients and

limited facilities to timely interventional procedures, such as kidney biopsy, for diagnosis of underlying disorders. This may contribute in low prevalence of glomerular disease, which is essentially diagnosed by kidney biopsy, in some countries including Islamic republic of Iran. Advanced diagnostic skills and tools play important roles in reporting of more accurate statistical data concerning this issue.

In The United States, while rates of ESRD due to glomerulonephritis have declined among both whites and African Americans younger than 40, the same is not true for ESRD due to diabetes and hypertension in those age 20–39. The linear rate of increase in diabetic ESRD among African Americans is particularly noteworthy, in part because of its contrast to the decline seen among whites, for whom the rate has fallen to the level noted 15 years ago. Potential factors involving the rising prevalence in the African Americans and other minority populations are linked to greater degrees of obesity in the population overall and among minorities. Although rates of incident ESRD due to diabetes have increased among younger patients, they have been stable or falling in older populations and whites, showing that a detailed assessment of subpopulations is required to determine whether trends are consistent across all groups defined by age, gender, race and primary cause of ESRD [2].

Preparation for and initiation of renal replacement therapy

It is important to identify patients who require renal replacement therapy since adequate preparation can decrease morbidity and mortality. Early identification affords initiation of dialysis at the optimal stage and may also allow the evaluation of family members for the renal transplantation prior to the need for dialysis. Furthermore, adequate time must be spent in order to psychological acceptance for the requirement of life-long renal replacement therapy by the ESRD patient [15].

Referral to nephrologists

The practice of nephrology encompasses both primary (nonrenal related) and specialty medical care. There are controversial factors over primary care provided by a nephrologist including [16]:

- The time and training required for primary care
- The lack of adequate reimbursement for non-dialysis-related care
- The availability of nephrologists
- Impending systems of global capitation for dialysis care

There is little information regarding the effect of nephrologist's role as a primary care provider, on the morbidity and mortality of ESRD patients. Some evidences suggest that patient outcome may be influenced by the expertise of the physician and some not [17]. Although, in clinical practice nephrologists involve in the primary care of the dialysis patients however; with the growing populations with end-stage renal disease, fewer nephrologists may be acting as primary care providers for their dialysis patients.

Effectiveness and cost

Little information exists regarding the effectiveness and cost benefits with the care of ESRD patients by nephrologists versus internists [18]. One study on 174 hemodialysis patients showed that care provided by a nephrologist had been associated with a significantly lower length of hospitalization and lower costs and multiple lines

Cause	Prevalence (%)		
	United States	Iran	Saudi Arabia
Diabetes mellitus	40	26.8	25.2
Hypertension	28	13.5	30.4
Glomerular diseases	12.2	6.5	12.5
Cystic kidney disease	3.3	10.3	4.5
Tubulointerstitial disease	3.9	1.5	1.8
Unknown etiology	9	29.5	19.9

From: Afshar et al. [14]

Table 1: Underlying causes of chronic kidney disease (CKD).

of evidence support the finding that the timing of referral to the nephrologist influences outcome and cost of dialytic therapy [19]. As a result, patients with chronic kidney disease should be referred to a nephrologist early in the course of their disease, preferably before the plasma creatinine concentration exceeds 1.2 and 1.5 mg/dL in women and men, respectively, or the eGFR (estimated glomerular filtration rate) is less than 60 mL/min per 1.73 m² [20].

Choice of renal replacement therapy

Once it is determined that renal replacement therapy will be necessary, the patient should be informed to consider the advantages and disadvantages of hemodialysis, peritoneal dialysis (PD) and renal transplantation [21]. The 2006 NKF-K/DOQI guidelines recommend that patients with a GFR less than 30 mL/min per 1.73 m² should be educated about these issues [20]. Kidney transplantation is the treatment of choice for ESRD. Compared with maintenance dialysis, renal transplantation improves the quality of life and reduces the mortality risk of most patients. Referral to a transplant program should occur once renal replacement therapy is thought to be required within the next year [22].

For these individuals and for those who are suitable transplant recipients but must wait for an available kidney, the choice between hemodialysis or PD is influenced by a number of considerations such as availability, convenience, comorbid conditions, home situation, age, gender, and the ability to tolerate volume shifts.

In developed countries, the universal availability of renal replacement therapy facilitates its application in every patient in whom it might be indicated. However, some patients including the elderly and terminally ill, may refuse dialysis. Nevertheless, not all nephrologists are willing to recommend no treatment, especially when dialysis facilities are available with no need to ration therapy. These issues can be a source of conflict among physicians, patients, and their families.

Ethical issues

Ethical issues concerning the renal replacement therapy are drawing increasing attention within the nephrology community. Many nephrologists have questioned why the prevalence of renal replacement therapy is higher in some countries such as the United States when compared to other countries. This difference may be attributed to a number of factors, including:

- Refusal for treatment by the patient due to religious or personal believe such as “A dead person is ruined by organ transplantation” or “The spirit of a dead person is not at peace if their organs live in the body of another person” [23].
- Limited knowledge and understanding of renal disease in ESRD population.
- Poor communication among the patient, the patient’s family, and the physician.
- Funding or policy restrictions on dialysis process.

Inadequate knowledge about the disease status and patient’s rights can lead to conflicts between all concerned groups. Most of these conflicts can be resolved if the patient and physician have clear communication and full understanding of the medical situation.

Treatment Options for ESRD

Hemodialysis: Hemodialysis is the predominant modality for

treatment of ESRD throughout the world. In the United States, 91% of patients start their ESRD care with hemodialysis [2]. This therapeutic modality can be performed in “short daily” or “long nocturnal” manner. The nocturnal dialysis sessions are usually 8-10 hours in length that can be delivered either at home or in-center. Most patients on nocturnal hemodialysis dialyze 5-6 nights per week, giving 40-50 hours of treatment per week (compared to 12 hours in a short daily schedule). In general, patients treated with home hemodialysis lead more independent lives, have better rehabilitation and have higher survival outcomes than those treated with other dialysis modalities. This is due in part to home hemodialysis patients generally getting more adequate dialysis than those treated in center. Additional benefits include the assumption of more individual responsibility for performing the treatment and a diminished role for dialysis in the patient’s life [24].

Hemodialysis is generally well tolerated, although ultrafiltration can cause hypotension, nausea and muscle cramps [25]. Older patients and those with established cardiovascular disease may tolerate the procedure less well. Vascular access failure and the need for intermittent heparinization are additional problems, particularly in diabetic patients.

Peritoneal dialysis: Peritoneal dialysis is another renal replacement therapy modality which due to its simplicity, offers patients a home-based therapy with very little requirement for special water systems and simple equipment setup time. In the United States, 11% of patients undergo PD, whereas in Australia and Canada, this percentage reaches to 40% and 20%-30% of dialysis patients, respectively [26]. Compared with hemodialysis, PD has the following advantages:

- Maintenance of relatively constant blood levels of urea nitrogen, creatinine, sodium and potassium.
- Hematocrit levels higher than hemodialysis patients.
- Better hemodynamic stability due to gradual ultrafiltration.
- Promotion of patient independence.
- More efficiency for large solute removal.
- No need for patient heparinization.

Indeed, with few exceptions, hemodialysis has no medical advantage over PD. Both effectively manage the consequence of uremia. Psychosocial and individual lifestyle issues should be considered when selecting a particular mode of dialysis. Home hemodialysis provides an opportunity for independence, but it can cause emotional stress for the dialysis assistant or family members. Furthermore, in some home settings, neither hemodialysis nor peritoneal dialysis is advisable. On the other hand, in-center hemodialysis can provide ongoing social interaction for older, single patients who have few friends or family members available to provide support [2].

Transplantation: Transplantation of the human kidney is frequently the most effective treatment of advanced chronic renal failure. At present, mean 1-year graft survival for all types of living donor transplants is approximately 95%. In many centers, it is 90% or greater for all match grades of deceased donor transplants [2]. Mortality rates after transplantation are highest in the first year and are age-related: 2% for ages 18 to 34 years, 3% for ages 35 to 49 years and 6.8% for ages over 50 to 60 years. These rates compare favorably to those in the chronic dialysis population, even after risk adjustments for age, diabetes and cardiovascular status. Overall, transplantation returns

the majority of patients to an improved lifestyle and an improved life expectancy, as compared to patients on dialysis [2].

In countries which deceased donor transplantation constitutes the major renal transplantation pool, the critical shortage of donor organs is the main limitation to expanding the use of this modality. Despite steady rise in the dialysis population (e.g. approximately 5% in USA and 17% in Iran, each year), the annual rate of deceased kidney donation has remained constant [1,2]. In the prevalent population, the number waiting to receive a transplant reached 77,695 in 2008, with a one-year growth of 5.8 percent [2]. Fortunately in recent years, living donor transplantation has increased even greater than the deceased donor transplants, however, these transplants are mainly of unrelated type and there is a gap between the supply of and the demand for kidney donation. Expansion of the donor pool by overcoming immunological barriers, such as ABO incompatibility and positive cross-matches, would expand the availability of organs considerably and ultimately reduce mortality in patients with end-stage renal failure. ABO-incompatible renal transplantation has been attempted since the early 1970. Today, Japan has the largest experience of this type of renal transplantation in the world due to the serious shortage of deceased donor kidneys in that country. However, even in countries with well developed deceased-donor procurement activities, as many as 15–20% of potential living donors are excluded because of ABO incompatibility [27]. Now, using an innovative desensitization technique, it can be possible to eliminate a recipient's reaction to an incompatible blood type, allowing more people to receive and benefit from a kidney transplant from their friend, spouse, or family member. In the daisy chain transplant program (since the 2008), a so-called altruistic donor is needed to give a kidney to one person who doesn't have any match in the chain. The donor is considered altruistic because she/he is giving up a kidney without receiving one for a loved one in exchange. Medical professionals are able to match donors and recipients within a pool of candidates based on the crucial characteristics of blood and tissue antigens [28].

The increase in living donor transplantation may be the result of technical advances in harvesting the donor kidney, especially with the use of laparoscopic organ harvesting that has led to a reduction in patient discomfort and recovery time. Donor characteristics differ in deceased versus living donors. Deceased donation rates are highest in donors aged 45 to 59 years old and in men compared with women; rates are higher for whites than for blacks and lowest in Asians. In contrast, living donation rates are highest in older donors (those aged 60–69), higher in women than in men and similar in whites and blacks and higher in Asians. Attempts to increase the number of deceased donor transplants have led to several novel strategies including the use of less optimal allografts [29]. In Iran, as the first country in total counts of kidney transplantation operations per year in the Middle East, the main pool of kidney donors consists of living donors (unrelated 78% and related 6%) and deceased kidney donation supplies only 16% of total renal transplantations [1]. In addition, the rate of renal transplantation varies considerably among patient groups. Transplantation rate is dependent to various factors including, age, race, gender, insurance status, and type of dialysis center. Substantial racial differences exist in renal replacement therapy, for example, white patients make up 55% of prevalent hemodialysis patients but 75% of the prevalent transplant population, whereas, African Americans account for 38% of prevalent hemodialysis population but only 18% of the transplant population [29]. Transplant rates are highest in patients aged less than 18 years and decrease with advancing age. Rates have remained relatively constant

in subjects aged less than 50 years but have doubled over the last decade in those aged 50 to 64 and tripled in those aged 65 and older. Striking gender and racial inequalities remain in current transplant rates, with male patients being wait listed and transplanted relatively more frequently than females and white patients being several fold more likely to receive a transplant than blacks. The racial disparities in transplantation rates appear to stem from both clinical characteristics that appropriately influence the subjects' candidacy for transplantation and apparent overutilization in whites and underutilization in blacks. These inequalities have narrowed somewhat over time as transplant rates in whites and males have decreased, while those in blacks and in women have remained steady [30].

Patient survival: Selection of the most appropriate therapeutic option for patients with ESRD is based on the comparison of survival rates among various treatment modalities. Such comparisons are relatively difficult because data in the literature often do not reflect the fact that patients change treatment modalities frequently and that the characteristics of patients selected for each modality may differ substantially when therapy is begun. Most of the data comparing survival rates suggest that an individual's state of health before treatment, rather than the treatment modality itself, is the most important factor in determining survival [31].

For dialysis patients, a number of comorbid factors can adversely affect survival [32]; these include increased age, diabetes, coronary artery disease, chronic obstructive pulmonary disease, duration on dialysis (vintage) and cancer [33]. Generally, blacks have a better survival rate on dialysis than do nonblacks, whereas certain renal diseases, such as amyloidosis, multiple myeloma and renal cancer, are associated with poorer prognoses. Nutritional status has been increasingly recognized as an important predictor of survival during long-term dialysis [34]. If these factors are not considered, accurate comparisons among therapeutic modalities cannot be made.

Although, survival rates for patients treated with either dialysis or transplantation have steadily improved over time due to better pre-ESRD care and widespread provision of higher dialysis doses, however, despite much progress, still remain markedly reduced compared with rates in the general population. Renal replacement therapy prolongs life but does not restore a normal life expectancy [35]. Recent data from the USRDS suggests that long-term outcomes for hemodialysis patients may be getting worse, even after adjusting for changing demographics and comorbidities in the hemodialysis population. Thus, an examination of the future of renal replacement therapy is timely and indicated. Among the most common causes of kidney disease, only diabetes mellitus has an adverse effect on patient survival [31]. Other common causes of renal failure do not significantly affect survival. The survival rate of patients with ESRD caused by other less-common renal diseases, such as collagen vascular disease and vasculitis, is generally similar to that of nondiabetic patients with common causes of ESRD. Not surprisingly, systemic and renal malignancies are associated with a poor prognosis. Future studies in dialysis should invest the necessary resources to include repeated assessments of comorbidity.

Conclusion

The epidemiology of chronic kidney disease has advanced into recognition of the high prevalence of earlier stages of CKD marked by kidney damage and moderate reductions in GFR. The epidemiology of treated kidney failure is more mature, with widely available data internationally showing a progressive increase in all countries, so that

the total number of cases requiring dialysis is projected to continue increasing substantially. Outcomes after dialysis are better for patients who start early rather than late [36] and who start electively rather than emergently. However, some investigator reported that early initiation of dialysis in patients with stage-5 chronic kidney disease was not associated with an improvement in survival or clinical outcomes [37]. Hemodialysis is the mainstay of treatment for ESRD and the ever-increasing numbers of ESRD patients worldwide present a challenge to healthcare providers to optimize treatment outcomes in the most cost-effective manner. The results of the HEMO Study, in which increasing the delivered dose of dialysis or using high-flux dialyzer membranes did not improve mortality, suggests that new approaches will be required to improve overall mortality and morbidity rates in this modality [38].

Predialysis or preemptive transplantation is the preferred therapeutic modality for ESRD in terms of morbidity, mortality and long-term graft survival, but only 2% of ESRD patients receive preemptive transplantation [2]. The very long waiting time for deceased donor organs makes it unlikely that an ESRD patient without a living donor will be allocated for preemptive transplantation.

However, hemodialysis attempts to recapitulate glomerular filtration but not replace renal tubular function. Tubular processing of glomerulofiltrate via selective metabolism and transport may be essential in mitigating uremic toxicity. Cell-based therapies providing proximal tubular function are in development in the treatment of patients with renal failure. Ultimately, partial or complete renal organogenesis may lead to successful renal replacement therapy without the allogenicity or xenogenicity associated with heterotopic transplantation [39].

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